Novel Synthesis of Nine-Membered Oxa-Heterocycles by Pd(0)-Catalyzed Intramolecular Heck Reaction via Unusual 9-*endo-trig*-Mode Cyclization

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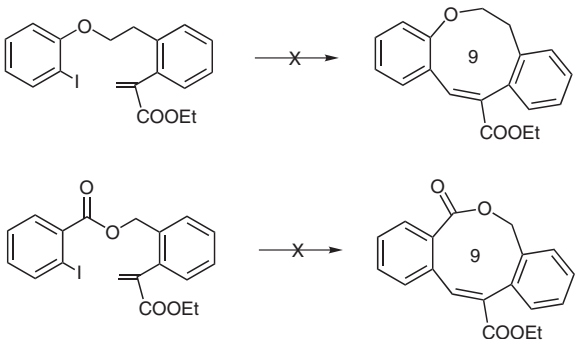
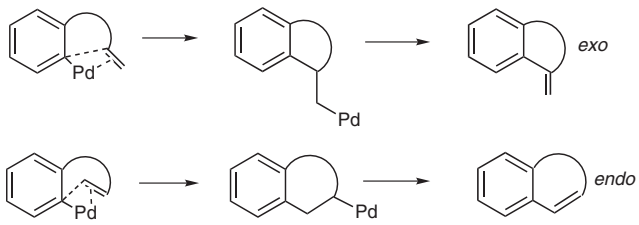
Abstract: Syntheses of nine-membered oxa-heterocyclic compounds by the application of the intramolecular Heck reaction have been difficult to develop. Herein, we describe the synthesis of this class of compounds through the 9-*endo-trig* cyclization and 8-*endo-trig* cyclization, respectively – a rare mode of cyclization in the literature.

Key words: Claisen rearrangement, intramolecular Heck reaction, 9-*endo-trig*, $Pd(OAc)_2$ catalyst, oxa-heterocycles, medium-sized ring compounds

During the final quarter of the twentieth century, palladium catalysts emerged as extremely powerful tools for the construction of carbon–carbon, as well as carbon–heteroatom bonds.[1] Numerous monographs and review articles have documented[1,2] the increasing frequency with which palladium-catalyzed coupling processes are applied to a wide array of endeavors, which range from synthetic organic chemistry to material science. Their popularity stems in part from their tolerance of different functional groups, which allows them to be employed in the synthesis of highly complex molecules.[2] Generally, many natural products, as for examples rhazinilam[3] and its congener rhazinal[4] that contain medium-sized heterocyclic rings fused to aryl rings, have attracted considerable attention in both the biological and synthetic communities.[5] The formation of medium-sized rings via intramolecular Heck reaction has been rare. Furthermore Negishi et al. supported[6] the lack of formation of a nine-membered ring by the cyclic Heck reaction and reported only a 2% yield. Recently, Majumdar et al. have reported[7] the synthesis of medium-sized ring compounds, mainly seven- and eight-membered, based on the ring-closing metathesis reactions and Guy et al. reported the synthesis of seven- and eight-membered heterocyclic ring[8] fused with aryl rings by the application of intramolecular Heck reaction. Guy et al. also tried to synthesize nine-membered ring by the same reaction. But, unfortunately their attempts to apply the intramolecular Heck reaction protocol to the synthesis of nine-membered ring failed (Scheme 1).



Scheme 1 Attempted scheme for the synthesis of nine-membered ring



Scheme2 Mode of *exo-trig* and *endo-trig* cyclization

In the intramolecular Heck reaction, entropic factors dominate and control the mode of cyclization. In the majority of studied cases, this reaction proceeded in the *exo-trig* mode, as this way is by far less sterically[9] demanding. The *endo-trig* mode requires the olefinic bond to move inside the loop in the intermediate π-complex, which requires a much more flexible tether between it and the aromatic ring to be able to bend freely into the proper conformation (Scheme 2) and is highly improbable due to geometric reasons.[9]

This has prompted us to undertake a study on the phosphine-free[10] Pd(0)-catalyzed intramolecular Heck[11] reaction of different 6-allyl-1,3-dimethyl-5-(2′-bromoaryloxymethyl)uracil derivatives with a view to synthesize nine-membered oxa-heterocycles fused with a benzene and uracil moieties synthetically, which is a challenge due to the presence of strain within such compounds. Additional interest is derived from our continued efforts on the synthesis of heterocycles annulated with bioactive moieties[7a] and pyrimidine system is well known for its bioactivity.[12]

The required Heck precursors **4a–f** for our present study were synthesized in 85–96% yields by refluxing 1,3-dimethyl-6-allyl-5-hydroxyuracil **3a–c**[13] with different allyl

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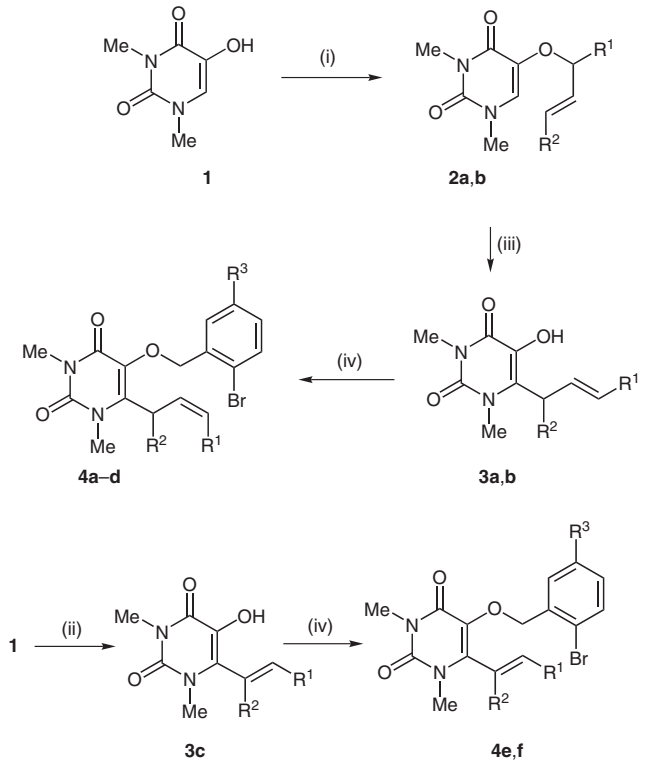


Scheme 3 *Reagents and conditions*: (i) allylbromide, K_2CO_3, acetone, NaI; (ii) cinnamyl bromide, K_2CO_3, acetone, NaI; (iii) chlorobenzene, reflux; (iv) benzylbromide, acetone, K_2CO_3, NaI.

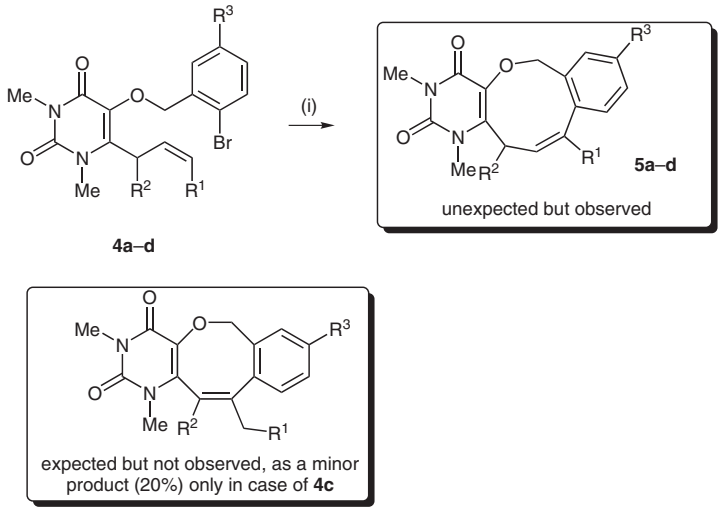
bromides in dry acetone for about 2–3 hours in the presence of anhydrous potassium carbonate and a small amount of sodium iodide (Finkelstein conditions[14]). The compounds **3a–c** in turn were prepared in good yields by the reaction of 5-hydroxyuracil with allyl bromide followed by [3,3]-sigmatropic rearrangement in refluxing chlorobenzene[15] for 1–1.5 hours (Scheme 3). In the case of compound **3c**, O-alkylation with cinnamyl bromide, [3,3]-sigmatropic rearrangement and double-bond isomerization occur simultaneously in a single step in acetone at refluxing conditions. The results are summarized in Table 1.

Table 1 Yields of the Starting Materials **4a–f**

Entry	Starting materials	R^1	R^2	R^3	Yield (%)
1	**4a**	H	Me	H	93
2	**4b**	H	Me	OMe	89
3	**4c**	H	H	H	96
4	**4d**	H	H	OMe	87
5	**4e**	Me	Ph	H	91
6	**4f**	Me	Ph	OMe	85

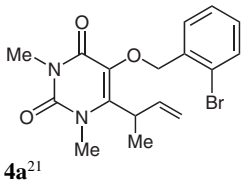
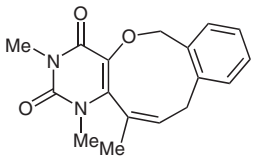
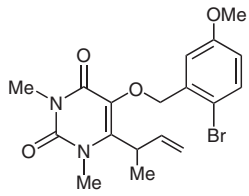
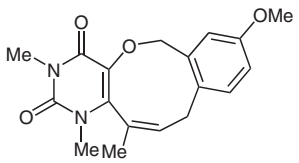
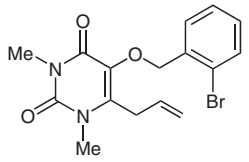
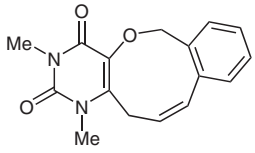
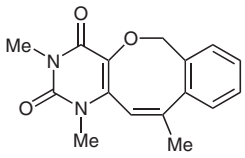
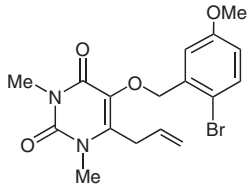
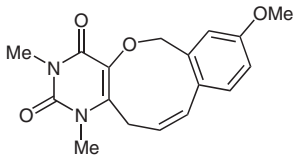
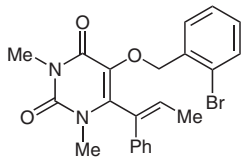
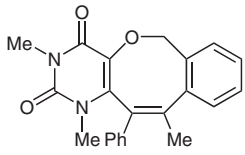
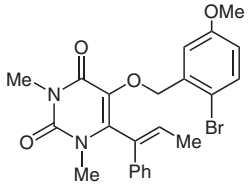
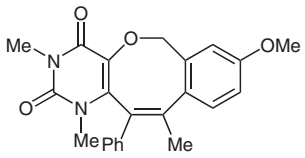
The intramolecular Heck reactions were performed[16] in dry *N*,*N*-dimethylformamide (DMF) using potassium acetate as a base, tetrabutylammoniumbromide (TBAB) as a promoter,[17] and $Pd(OAc)_2$ as catalyst under nitrogen atmosphere at 100 °C for about 2–3.5 hours. All reactions gave the *endo*-Heck heterocyclic ring compounds **5a–f** fused with aryl ring and uracil moiety by the unusual 9-*endo* and 8-*endo* cyclization mode exclusively in 88–96% yield except for compound **4c**. Compound **4c** gave the 9-*endo* product **5c** (74%) along with the formation of the eight-membered ring compound **6a** (12%) by the 8-*exo*-cyclization mode (Scheme 4). The results are summarized in Table 2.

The intramolecular Heck reaction has two modes of ring closure, i.e. *exo* and *endo* cyclization. A large-size ring (ca. 20) formation with a flexible tether generally favours[18] *endo* cyclization and small to medium-size ring formation usually *exo* cyclization since the corresponding *endo* cyclization is very demanding. In our present cases, the mechanistic interpretation for the formation of the 8-*exo-trig* cyclization mode[19] is quite reasonable because of the less steric demand. But the formation of the products **5a–f**, i.e. the nine-membered rings and eight-membered



Scheme 4 Synthesis of nine-membered ring compounds by the intramolecular Heck reaction. *Reagents and conditions*: (i) dry DMF, 10 mol% $Pd(OAc)_2$, KOAc (2.75 equiv), TBAB (1.2 equiv), N_2 atmosphere.

Table 2 Summarized Results of the Heck Reactions

Entry	Substrate	Product
1	 **4a**[21]	 **5a**[22] (90%)
2	 **4b**	 **5b** (94%)
3	 **4c**	 **5c** (74%)
		 **6a**[23] (12%)
4	 **4d**	 **5d** (96%)
5	 **4e**	 **5e** (88%)
6	 **4f**	 **5f** (92%)

rings by the 9-*endo-trig* and 8-*endo-trig* cyclization mode is quite interesting.

Generally in those cases when the *endo* mode is favored for electronic reasons (e.g., if the substrate going into the cyclization contains a Michael-type olefinic fragment in the intramolecular Heck reaction) the reaction can lead to larger cycles. The need for a more flexible chain is likely to explain why the yield of the *endo* cyclization product steadily grows with longer chain length – a behavior not common in the cyclization chemistry.[20] Interestingly, in our present cases the nine-membered rings are obtained in excellent yields (which Guy et al. failed to synthesize) by the 9-*endo-trig* cyclization mode. To our knowledge this mode of cyclization is rare in the literature.[20]

In conclusion, we have developed a general strategy for the synthesis of nine-membered ring using transition-metal catalysis by the unusual 9-*endo trig* cyclization mode. This method has a lot of advantage because this strategy is straightforward and offers a convergent synthesis of tricyclic compounds containing nine-membered rings. The tolerance of various functional groups on the substrates is another advantage of this protocol. Implementation of this strategy to the synthesis of a heterocyclic library is under way and will be reported in due course.

Acknowledgment

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(16) **General Procedure for the Synthesis of Compounds 5a–f and 6a**

A mixture of the compound **4a** (100 mg, 0.265 mmol), TBAB (1.2 equiv), dry KOAc (2.75 equiv) was taken in dry DMF (10 mL) under nitrogen atmosphere. Then, the catalyst $Pd(OAc)_2$ (10 mmol%, 5.92 mg) was added and the mixture was stirred in an oil bath at 100 °C for about 2–3.5 h. The reaction mixture was cooled, and H_2O (3 mL) was added. It was extracted with EtOAc (3 × 10 mL) and washed with H_2O (2 ×10 mL), followed by brine (15 mL). The organic layer was dried (Na_2SO_4) and evaporation of EtOAc furnished the crude mass, which was purified by column chromatography over silica gel. Elution of the column with 10% EtOAc–PE afforded the product **5a**. Similarly, the other substrates **4b–f** were subjected to the reaction under the same conditions to give products **5b–f** and **6a**.

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(21) **Synthesis of the Precursors 4a–f; Typcial Procedure**

A mixture of compound **3** and different 2-bromobenzylbromides and dry K_2CO_3 (2.0 mg) in dry acetone (75 mL) in the presence of NaI was refluxed for a period of 2–3 h. After cooling the reaction mixture was filtered and the solvent was removed. The residual mass was extracted with $CHCl_3$, washed with H_2O, followed by brine–H_2O, and dried (Na_2SO_4). Removal of $CHCl_3$ gave a crude product, which was chromatographed over silica gel (60–120 mesh). Elution of the column with PE–EtOAc (2:1) gave compounds **4a–f**.

Compound **4a**: yield 93%, white solid, mp 101–102 °C. IR (KBr): ν_{max} = 1649, 1701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.24 (d, 3 H, =CHCH_3, *J* = 7.2 Hz), 3.32 (s, 3 H, NCH_3), 3.39 (s, 3 H, NCH_3), 4.28–4.31 (m, 1 H, =C*H*CH_3), 5.02 (dd, 1 H, =CHC$H_a$$H_b$, *J* = 2.1, 17.4 Hz), 5.11 (dd, 1 H, =CHC$H_a$$H_b$, *J* = 2.1, 12.2 Hz), 5.12 (s, 2 H, OCH_2), 5.72–5.80 (m, 1 H, CH_2=C*H*), 7.18 (dt, 1 H, ArH, *J* = 1.6, 7.7 Hz), 7.31 (dt, 1 H, ArH, *J* = 1.0, 7.4 Hz), 7.51–7.56 (m, 2 H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.1, 28.1, 33.2, 34.0, 73.0, 115.6, 123.5, 127.4, 129.6, 130.0, 130.8, 132.5, 135.9, 137.7, 147.7, 151.3, 157.6. MS: *m/z* = 378 [M^+], 380 [M^+ + 2]. Anal. Calcd (%) for $C_{17}H_{19}BrN_2O_3$: C, 53.84; H, 5.05; N, 7.39. Found: C, 53.88; H, 5.09; N, 7.23.

(22) **Synthesis of Compounds 5a–f and 6a; General Procedure**

A mixture of the compound **4a** (100 mg, 0.265 mmol), TBAB (1.2 equiv), dry KOAc (2.75 equiv) was taken in dry DMF (10 mL) under nitrogen atmosphere. Then, the catalyst $Pd(OAc)_2$ (10 mmol%, 5.92 mg) was added and the mixture was stirred in an oil bath at 100 °C for about 2–3.5 h. The reaction mixture was cooled, and H_2O (3 mL) was added. It was extracted with EtOAc (3 × 10 mL), washed with H_2O (2 × 10 ml), and followed by brine (15 mL). The organic layer was dried (Na_2SO_4), evaporation of EtOAc furnished the crude mass, which was purified by column chromatography over silica gel. Elution of the column with 10% EtOAc–PE afforded the product **5a**. Similarly, the other substrates **4b–f** were subjected to the reaction under the same conditions to give products **5b–f** and **6a**.

Compound **5a**: yield 90%, white solid, mp 193–194 °C. IR (KBr): ν_{max} = 1648, 1700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.84 (s, 3 H, =CCH_3), 3.27 (d, 2 H, =CHCH_2, *J* = 8.6 Hz), 3.35 (s, 3 H, NCH_3), 3.43 (s, 3 H, NCH_3), 4.65 (d, 1 H, OC$H_a$$H_b$, *J* = 12.6 Hz), 5.40 (d, 1 H, OC$H_a$$H_b$, *J* = 12.6 Hz), 5.87 (t, 1 H, *J* = 8.6 Hz, CH_2C*H*), 7.24–7.27 (m, 2 H, ArH), 7.32–7.36 (m, 2 H, ArH). ^{13}C NMR (135 mode, $CDCl_3$): δ = 21.9, 28.6, 34.4, 36.7, 77.2, 123.3, 127.3, 129.5, 130.3, 130.6, 132.0, 133.9, 137.1, 138.5, 143.5, 151.9, 161.1. DEPT (135 mode, $CDCl_3$): δ = 21.9, 28.6, 34.4, 36.7 (CH_2), 77.2 (OCH_2), 127.3, 129.5, 130.3, 130.6, 133.9. HRMS: *m/z* calcd: 299.1406 [M + H], 321.1250 [Na + H]. Found: 299.1448 [M + H], 321.1224 [Na + H]. Anal. Calcd (%) for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.59; H, 6.07; N, 9.55.

The benzylic CH_2 protons appear at δ = 4.65 and 5.40 ppm perhaps due to the slow exchange of the two nine-membered ring conformers in NMR time scale. However, DEPT (135 mode) experiment showed that the CH_2 carbon is present in benzylic CH_2O moiety. This was again confirmed by HMBC and COSY experiments.

(23) Compound **6a**: yield 12%, viscous liquid. IR (neat): ν_{max} = 1648, 1701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.34 (s, 3 H, =CHCH_3), 3.21 (s, 3 H, NCH_3), 3.27 (s, 3 H, NCH_3), 5.24 (s, 2 H, OCH_2), 6.02 (s, 1 H, =CH), 7.19–7.25 (m, 2H, ArH), 7.26–7.33 (m, 2 H, ArH). MS: *m/z* = 284 [M^+]. Anal. Calcd (%) for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.71; H, 5.66; N, 9.88.